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L11: Entry 11 of 17 File: USPT Nov 16, 1999

DOCUMENT-IDENTIFIER: US 5985309 A
TITLE: Preparation of particles for inhalation

Abstract Paragraph Left (1):
Particles incorporating a surfactant and/or a hydrophilic or hydrophobic complex of a positively or negatively charged therapeutic agent and a charged molecule of opposite charge for drug delivery to the pulmonary system, and methods for their synthesis and administration are provided. In a preferred embodiment, the particles are made of a biodegradable material and have a tap density less than 0.4 g/cm.sup.3 and a mass mean diameter between 5 .mu.m and 30 .mu.m, which together yield an aerodynamic diameter of the particles of between approximately one and three microns. The particles may be formed of biodegradable materials such as biodegradable polymers. For example, the particles may be formed of poly(lactic acid) or poly(glycolic acid) or copolymers thereof. Alternatively, the particles may be formed solely of a therapeutic or diagnostic agent and a surfactant. Surfactants can be incorporated on the particle surface for example by coating the particle after particle formation, or by incorporating the surfactant in the material forming the particle prior to formation of the particle. Exemplary surfactants include phosphoglycerides such as dipalmitoyl phosphatidylcholine (DPPC). The particles can be effectively aerosolized for administration to the respiratory tract to permit systemic or local delivery of wide a variety of therapeutic agents. Formation of complexes of positively or negatively charged therapeutic agents with molecules of opposite charge can allow control of the release rate of the agents into the blood stream following administration.

Brief Summary Paragraph Right (2):
Aerosols for the delivery of therapeutic agents to the respiratory tract have been described, for example, Adjei, A. and Garren, J. Pharm. Res., 7: 565-569 (1990); and Zanen, P. and Lamm, J. -W. J. Int. J. Pharm., 114: 111-115 (1995). The respiratory tract encompasses the upper airways, including the oropharynx and larynx, followed by the lower airways, which include the trachea followed by bifurcations into the bronchi and bronchioli. The upper and lower airways are called the conducting airways. The terminal bronchioli then divide into respiratory bronchioli which then lead to the ultimate respiratory zone, the alveoli, or deep lung. Gonda, I. "Aerosols for delivery of therapeutic and diagnostic agents to the respiratory tract," in Critical Reviews in Therapeutic Drug Carrier Systems, 6:273-313 (1990). The deep lung, or alveoli, are the primary target of inhaled therapeutic aerosols for systemic drug delivery.

Brief Summary Paragraph Right (3):
Inhaled aerosols have been used for the treatment of local lung disorders including asthma and cystic fibrosis (Anderson et al., Am. Rev. Respir. Dis., 140: 1317-1324 (1989)) and have potential for the systemic delivery of peptides and proteins as well (Patton and Platz, Advanced Drug Delivery Reviews, 8: 179-196 (1992)). However, pulmonary drug delivery strategies present many difficulties for the delivery of macromolecules; these include protein denaturation during aerosolization, excessive loss of inhaled drug in the oropharyngeal cavity (often exceeding 80%), poor control over the site of deposition, lack of reproducibility of therapeutic results owing to variations in breathing patterns, the frequent too-rapid absorption of drug potentially resulting in local toxic effects, and phagocytosis by lung macrophages.

Brief Summary Paragraph Right (4):
Considerable attention has been devoted to the design of therapeutic aerosol inhalers to improve the efficiency of inhalation therapies. Tinsina et. al., Int. J. Pharm., 101: 1-13 (1995); and Tansey, I. P., Spray Technol. Market, 4: 26-29 (1994). Attention has also been given to the design of dry powder aerosol surface texture, regarding

particularly the need to avoid particle aggregation, a phenomenon which considerably diminishes the efficiency of inhalation therapies. French, D. L., Edwards, D. A. and Niven, R. W., J. Aerosol Sci., 27: 769-783 (1996). Dry powder formulations ("DPFs") with large particle size have improved flowability characteristics, such as less aggregation (Visser, J., Powder Technology 58: 1-10 (1989)), easier aerosolization, and potentially less phagocytosis. Rudt, S. and R. H. Muller, J. Controlled Release, 22: 263-272 (1992); Tabata, Y. and Y. Ikada, J. Biomed. Mater. Res., 22: 837-858 (1988). Dry powder aerosols for inhalation therapy are generally produced with mean diameters primarily in the range of less than 5 .mu.m. Ganderton, D., J. Biopharmaceutical Sciences, 3:101-105 (1992); and Gonda, I. "Physico-Chemical Principles in Aerosol Delivery," in Topics in Pharmaceutical Sciences 1991, Crommelin, D. J. and K. K. Midha, Eds., Medpharm Scientific Publishers, Stuttgart, pp. 95-115, 1992. Large "carrier" particles (containing no drug) have been co-delivered with therapeutic aerosols to aid in achieving efficient aerosolization among other possible benefits. French, D. L., Edwards, D. A. and Niven, R. W., J. Aerosol Sci., 27: 769-783 (1996).

Brief Summary Paragraph Right (5):
The human lungs can remove or rapidly degrade hydrolytically cleavable deposited aerosols over periods ranging from minutes to hours. In the upper airways, ciliated epithelia contribute to the "mucociliary escalator" by which particles are swept from the airways toward the mouth. Pavia, D. "Lung Mucociliary Clearance," in Aerosols and the Lung: Clinical and Experimental Aspects, Clarke, S. W. and Pavia, D., Eds., Butterworths, London, 1984. Anderson et al., Am. Rev. Respir. Dis., 140: 1317-1324 (1989). In the deep lungs, alveolar macrophages are capable of phagocytosing particles soon after their deposition. Warheit, M. B. and Hartsky, M. A., Microscopy Res. Tech., 26: 412-422 (1993); Brain, J. D., "Physiology and Pathophysiology of Pulmonary Macrophages," in The Reticuloendothelial System, S. M. Reichard and J. Filkins, Eds., Plenum, New York, pp. 315-327, 1985; Dorries, A. M. and Valberg, P. A., Am. Rev. Resp. Disease 146: 831-837 (1991); and Gehr, P. et al. Microscopy Res. and Tech., 26: 423-436 (1993). As the diameter of particles exceeds 3 .mu.m, there is increasingly less phagocytosis by macrophages. Kawaguchi, H. et al., Biomaterials 7: 61-66 (1986); Krenis, L. J. and Strauss, B., Proc. Soc. Exp. Med., 107:748-750 (1961); and Rudt, S. and Muller, R. H., J. Contr. Rel., 22: 263-272 (1992). However, increasing the particle size also has been found to minimize the probability of particles (possessing standard mass density) entering the airways and acini due to excessive deposition in the oropharyngeal or nasal regions. Heyder, J. et al., J. Aerosol Sci., 17: 811-825 (1986).

Brief Summary Paragraph Right (6):
Local and systemic inhalation therapies can often benefit from a relatively slow controlled release of the therapeutic agent. Gonda, I., "Physico-chemical principles in aerosol delivery," in: Topics in Pharmaceutical Sciences 1991, D. J. A. Crommelin and K. K. Midha, Eds., Stuttgart: Medpharm Scientific Publishers, pp. 95-117 (1992). Slow release from a therapeutic aerosol can prolong the residence of an administered drug in the airways or acini, and diminish the rate of drug appearance in the bloodstream. Also, patient compliance is increased by reducing the frequency of dosing. Langer, R., Science, 249:1527-1533 (1990); and Gonda, I. "Aerosols for delivery of therapeutic and diagnostic agents to the respiratory tract," in Critical Reviews in Therapeutic Drug Carrier Systems 6:273-313 (1990).

Brief Summary Paragraph Right (7):
Controlled release drug delivery to the lung may simplify the way in which many drugs are taken. Gonda, I., Adv. Drug Del. Rev., 5: 1-9 (1990); and Zeng, X. et al., Int. J. Pharm., 124: 149-164 (1995). Pulmonary drug delivery is an attractive alternative to oral, transdermal, and parenteral administration because self-administration is simple, the lungs provide a large mucosal surface for drug absorption, there is no first-pass liver effect of absorbed drugs, and there is reduced enzymatic activity and pH mediated drug degradation compared with the oral route. Relatively high bioavailability of many molecules, including macromolecules, can be achieved via inhalation. Wall, D. A., Drug Delivery, 2: 1-20 1995); Patton, J. and Platz, R., Adv. Drug Del. Rev., 8: 179-196 (1992); and Byron, P., Adv. Drug. Del. Rev., 5: 107-132 (1990). As a result, several aerosol formulations of therapeutic drugs are in use or are being tested for delivery to the lung. Patton, J. S., et al., J. Controlled Release, 28: 79-85 (1994); Damms, B. and Bains, W., Nature Biotechnology (1996);

Niven, R. W., et al., Pharm. Res., 12(9): 1343-1349 (1995); and Kobayashi, S., et al., Pharm. Res., 13(1): 80-83 (1996).

Brief Summary Paragraph Right (8):
Drugs currently administered by inhalation come primarily as liquid aerosol formulations. However, many drugs and excipients, especially proteins, peptides (Liu, R., et al., Biotechnol. Bioeng., 37:177-184 (1991)), and biodegradable carriers such as poly(lactide-co-glycolides) (PLGA), are unstable in aqueous environments for extended periods of time. This can make storage as a liquid formulation problematic. In addition, protein denaturation can occur during aerosolization with liquid formulations. Mumenthaler, M., et al., Pharm. Res., 11: 12-20 (1994). Considering these and other limitations, dry powder formulations (DPF's) are gaining increased interest as aerosol formulations for pulmonary delivery. Damms, B. and W. Bains, Nature Biotechnology (1996); Kobayashi, S., et al., Pharm. Res., 13(1): 80-83 (1996); and Timsina, M., et al., Int. J. Pharm., 101: 1-13 (1994). However, among the disadvantages of DPF's is that powders of ultrafine particulates usually have poor flowability and aerosolization properties, leading to relatively low respirable fractions of aerosol, which are the fractions of inhaled aerosol that escape deposition in the mouth and throat. Gonda, I., in Topics in Pharmaceutical Sciences 1991, D. Crommelin and K. Midha, Editors, Stuttgart: Medpharm Scientific Publishers, 95-117 (1992). A primary concern with many aerosols is particulate aggregation caused by particle-particle interactions, such as hydrophobic, electrostatic, and capillary interactions. An effective dry-powder inhalation therapy for both short and long term release of therapeutics, either for local or systemic delivery, requires a powder that displays minimum aggregation, as well as a means of avoiding or suspending the lung's natural clearance mechanisms until drugs have been effectively delivered.

Brief Summary Paragraph Right (9):
There is a need for improved inhaled aerosols for pulmonary delivery of therapeutic agents. There is a need for the development of drug carriers which are capable of delivering the drug in an effective amount into the airways or the alveolar zone of the lung. There further is a need for the development of drug carriers for use as inhaled aerosols which are biodegradable and are capable of controlled release of drug within the airways or in the alveolar zone of the lung. There also is a need for particles for pulmonary drug delivery with improved aerosolization properties.

Brief Summary Paragraph Right (10):
It is therefore an object of the present invention to provide improved carriers for the pulmonary delivery of therapeutic agents. It is a further object of the invention to provide inhaled aerosols which are effective carriers for delivery of therapeutic agents to the deep lung. It is another object of the invention to provide carriers for pulmonary delivery which avoid phagocytosis in the deep lung. It is a further object of the invention to provide carriers for pulmonary drug delivery which are capable of biodegrading and releasing the drug at a controlled rate. It is yet another object of the invention to provide particles for pulmonary drug delivery with improved aerosolization properties and optimized particle-particle interactions.

Brief Summary Paragraph Right (11):
Particles incorporating a surfactant and/or a hydrophilic or hydrophobic complex of a positively or negatively charged therapeutic agent and a charged molecule of opposite charge for delivery of therapeutic or diagnostic agents to the pulmonary system, and methods for their synthesis and administration, are provided. Exemplary surfactants include naturally occurring phosphatidylcholines, such as dipalmitoylphosphatidylcholine ("DPPC"). Exemplary hydrophilic or hydrophobic complexes include insulin (negatively charged) and protamine (positively charged). In a preferred embodiment, the particles are aerodynamically light particles, which are made of a biodegradable material, and have a tap density less than 0.4 g/cm.sup.3. The "aerodynamically light" particles generally have a mean diameter between 5 .mu.m and 30 .mu.m. The tap density less than 0.4 g/cm.sup.3 and mean diameter between 5 .mu.m and 30 .mu.m, are designed to yield particles with an aerodynamic diameter between approximately one and five microns, preferably between approximately one and three microns. The particles may be formed of biodegradable materials such as biodegradable polymers, proteins, or other water soluble or non-water soluble materials. Particles can also be formed of water-soluble excipients, such as trehalose or lactose, or proteins, such as the proteins to be delivered. In one embodiment, the particles

include only a therapeutic or diagnostic agent to be delivered to a patient in a complex with another charged molecule. In a second embodiment, the particles include only the agent and a surfactant. In a third embodiment, particles include surfactant and charged molecules forming a complex, which provides for sustained release.

Brief Summary Paragraph Right (12):
The particles can be used for enhanced delivery of a therapeutic agent to the airways or the alveolar region of the lung. The particles may be effectively aerosolized for administration to the respiratory tract to permit systemic or local delivery of a wide variety of therapeutic agents. They also optionally may be co-delivered with larger carrier particles, not carrying a therapeutic agent, having, for example, a mean diameter ranging between about 50 .mu.m and 100 .mu.m. The particles can be used to form a composition that includes the particles and a pharmaceutically acceptable carrier for administration to a patient, preferably for administration via inhalation.

Drawing Description Paragraph Right (1):
FIG. 1 is a graph comparing the mass fraction of the initial dose that is released from a dry powder inhaler device, after in vitro aerosolization of poly (D,L-lactic-co-glycolic acid) ("PLGA") microspheres made by a double emulsion procedure with and without the incorporation of L-.alpha.-phosphatidylcholine dipalmitoyl ("DPPC").

Drawing Description Paragraph Right (3):
FIG. 3 is a graph showing the aerosolization behavior of PLGA microspheres made by spray drying with and without the incorporation of DPPC showing the mass-fraction of the initial dose that is released from the dry powder inhaler device after in vitro aerosolization.

Drawing Description Paragraph Right (4):
FIG. 4 is a graph comparing the in vitro aerosolization behaviors of PLA and PLGA microspheres made by spray drying with and without the incorporation of DPPC showing the mass-fraction of the aerosolized dose that is deposited in stages of a cascade impactor corresponding to the "respirable-fraction".

Detailed Description Paragraph Right (3):
The particles can be used for controlled systemic or local delivery of therapeutic or diagnostic agents to the respiratory tract via aerosolization. Administration of the particles to the lung by aerosolization permits deep lung delivery of relatively large diameter therapeutic aerosols, for example, greater than 5 .mu.m in mean diameter. The particles can be fabricated with a rough surface texture to reduce particle agglomeration and improve flowability of the powder. The particles have improved aerosolization properties. The particle can be fabricated with features which enhance aerosolization via dry powder inhaler devices, and lead to lower deposition in the mouth, throat and inhaler device.

Detailed Description Paragraph Right (4):
The particles can be used to form a composition that includes the particles and a pharmaceutically acceptable carrier for administration to a patient, preferably for administration via inhalation. Suitable carriers include those typically used for inhalation therapy. Those of skill in the art can readily determine an appropriate pharmaceutically acceptable carrier for use in administering particles via inhalation.

Detailed Description Paragraph Right (14):
Surfactants which can be incorporated into particles to improve their aerosolization properties include phosphoglycerides. Exemplary phosphoglycerides include phosphatidylcholines, such as the naturally occurring surfactant, L-.alpha.-phosphatidylcholine dipalmitoyl ("DPPC"). The surfactants advantageously improve surface properties by, for example, reducing particle-particle interactions, and can render the surface of the particles less adhesive. The use of surfactants endogenous to the lung may avoid the need for the use of non-physiologic surfactants.

Detailed Description Paragraph Right (18):
Surfactants known in the art can be used including any naturally occurring surfactant.

Other exemplary surfactants include diphosphatidyl glycerol (DPPG); hexadecanol; fatty alcohols such as polyethylene glycol (PEG); polyoxyethylene-9-lauryl ether; a surface active fatty acid, such as palmitic acid or oleic acid; sorbitan trioleate (Span 85); glycocholate; surfactin; a poloxomer; a sorbitan fatty acid ester such as sorbitan trioleate; tyloxapol and a phospholipid.

Detailed Description Paragraph Right (21):
Polymeric particles may be prepared using single and double emulsion solvent evaporation, spray drying, solvent extraction, solvent evaporation, phase separation, simple and complex coacervation, interfacial polymerization, and other methods well known to those of ordinary skill in the art. Particles may be made using methods for making microspheres or microcapsules known in the art, provided that the conditions are optimized for forming particles with the desired aerodynamic diameter, or additional steps are performed to select particles with the density and diameter sufficient to provide the particles with an aerodynamic diameter between one and five microns, preferably between one and three microns.

Detailed Description Paragraph Right (27):
The polymeric particles are preferably prepared by spray drying. Prior methods of spray drying, such as that disclosed in PCT WO 96/09814 by Sutton and Johnson, disclose the preparation of smooth, spherical microparticles of a water-soluble material with at least 90% of the particles possessing a mean size between 1 and 10 .mu.m. The method disclosed herein provides rough (non-smooth), non-spherical microparticles that include a water-soluble material combined with a water-insoluble material. At least 90% of the particles possess a mean size between 5 and 30 .mu.m, and a low mass or tap density (less than 0.4 g/cc).

Detailed Description Paragraph Right (35):
The aerodynamically light particles, optionally incorporating a therapeutic or diagnostic agent, with a tap density less than about 0.4 g/cm.sup.3, mean diameters of at least about 5 .mu.m, and an aerodynamic diameter of between one and five microns, preferably between one and three microns, are more capable of escaping inertial and gravitational deposition in the oropharyngeal region, and are targeted to the airways or the deep lung. The use of larger particles (mean diameter at least about 5 .mu.m) is advantageous since they are able to aerosolize more efficiently than smaller, denser aerosol particles such as those currently used for inhalation therapies.

Detailed Description Paragraph Right (37):
Aerodynamically light particles thus are capable of a longer term release of an encapsulated agent in the lungs. Following inhalation, aerodynamically light biodegradable particles can deposit in the lungs (due to their relatively low tap density), and subsequently undergo slow degradation and drug release, without the majority of the particles being phagocytosed by alveolar macrophages. The drug can be delivered relatively slowly into the alveolar fluid, and at a controlled rate into the blood stream, minimizing possible toxic responses of exposed cells to an excessively high concentration of the drug. The aerodynamically light particles thus are highly suitable for inhalation therapies, particularly in controlled release applications.

Detailed Description Paragraph Right (38):
The preferred mean diameter for aerodynamically light particles for inhalation therapy is at least about 5 .mu.m, for example between about 5 and 30 .mu.m. The particles may be fabricated with the appropriate material, surface roughness, diameter and tap density for localized delivery to selected regions of the respiratory tract such as the deep lung or upper airways. For example, higher density or larger particles may be used for upper airway delivery, or a mixture of different sized particles in a sample, provided with the same or different therapeutic agent may be administered to target different regions of the lung in one administration.

Detailed Description Paragraph Right (41):
Inertial impaction and gravitational settling of aerosols are predominant deposition mechanisms in the airways and acini of the lungs during normal breathing conditions. Edwards, D. A., J. Aerosol Sci., 26: 293-317 (1995). The importance of both deposition mechanisms increases in proportion to the mass of aerosols and not to particle (or envelope) volume. Since the site of aerosol deposition in the lungs is determined by the mass of the aerosol (at least for particles of mean aerodynamic diameter greater

than approximately 1 .mu.m), diminishing the tap density by increasing particle surface irregularities and particle porosity permits the delivery of larger particle envelope volumes into the lungs, all other physical parameters being equal.

Detailed Description Paragraph Right (42):
The low tap density particles have a small aerodynamic diameter in comparison to the actual envelope sphere diameter. The aerodynamic diameter, d.sub.aer, is related to the envelope sphere diameter, d (Gonda, I., "Physico-chemical principles in aerosol delivery," in Topics in Pharmaceutical Sciences 1991 (eds. D. J. A. Crommelin and K. K. Midha), pp. 95-117, Stuttgart: Medpharm Scientific Publishers, 1992)), by the formula:

Detailed Description Paragraph Right (48):
The polymeric aerosols are useful as carriers for a variety of inhalation therapies. They can be used to encapsulate small and large drugs, release encapsulated drugs over time periods ranging from hours to months, and withstand extreme conditions during aerosolization or following deposition in the lungs that might otherwise harm the encapsulated therapeutic.

Detailed Description Paragraph Right (56):
Porous particles can be prepared which can be delivered via pulmonary delivery, and used, for example, for local or systemic delivery of incorporated agents and/or for imaging purposes. Particles incorporating diagnostic agents can be detected using standard techniques available in the art and commercially available equipment.

Detailed Description Paragraph Right (59):
Aerosol dosage, formulations and delivery systems may be selected for a particular therapeutic application, as described, for example, in Gonda, I. "Aerosols for delivery of therapeutic and diagnostic agents to the respiratory tract," in Critical Reviews in Therapeutic Drug Carrier Systems, 6:273-313, 1990; and in Moren, "Aerosol dosage forms and formulations," in: Aerosols in Medicine. Principles, Diagnosis and Therapy, Moren, et al., Eds, Esevier, Amsterdam, 1985.

Detailed Description Paragraph Right (65):
Aerodynamically light 50:50 PLGA particles were prepared by spray drying with testosterone encapsulated within the particles according to the following procedures. 2.0 g poly (D,L-lactic-co-glycolic acid) with a molar ratio of 50:50 (PLGA 50:50, Resomer RG503, B.I. Chemicals, Montvale, N.J.) and 0.50 g testosterone (Sigma Chemical Co., St. Louis, Mo.) are completely dissolved in 100 mL dichloromethane at room temperature. The mixture is subsequently spray-dried through a 0.5 mm nozzle at a flow rate of 5 mL/min using a Buchi laboratory spray-drier (model 190, Buchi, Germany). The flow rate of compressed air is 700 nl. The inlet temperature is set to 30.degree. C. and the outlet temperature to 25.degree. C. The aspirator is set to achieve a vacuum of -20 to -25 bar. The yield is 51% and the mean particle size is approximately 5 .mu.m. Larger particle size can be achieved by lowering the inlet compressed air flow rate, as well as by changing other variables. The particles are aerodynamically light, as determined by a tap density less than or equal to 0.4 g/cm.sup.3 and an aerodynamic diameter between one and five microns. Porosity and surface roughness can be increased by varying the inlet and outlet temperatures, among other factors.

Detailed Description Paragraph Right (67):
Aerodynamically light PLA particles with a model hydrophilic drug (dextran) were prepared by spray drying using the following procedure. 2.0 mL of an aqueous 10% w/v FITC-dextran (MW 70,000, Sigma Chemical Co.) solution was emulsified into 100 mL of a 2% w/v solution of poly (D,L-lactic acid) (PLA, Resomer R206, B.I. Chemicals) in dichloromethane by probe sonication (Sonics & Materials, Model VC-250 sonicator, Danbury, Conn.). The emulsion is subsequently spray-dried at a flow rate of 5 mL/min with an air flow rate of 700 nl/h (inlet temperature=30.degree. C., outlet temperature=21 .degree. C., -20 mbar vacuum). The yield is 56%.

Detailed Description Paragraph Right (69):
Aerodynamically light lysozyme particles were prepared by spray drying using the following procedure. 4.75 g lysozyme (Sigma) was dissolved in 95 mL double distilled water (5% w/v solution) and spray-dried using a 0.5 mm nozzle and a Buchi laboratory spray-drier. The flow rate of compressed air was 725 nl/h. The flow rate of the

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